INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

The Glucose-lowering Efficacy of Sitagliptin in Obese Japanese Patients with Type 2 Diabetes

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Abstract

Objective Dipeptidyl peptidase-4 (DPP-4) inhibitors are the most frequently prescribed oral hypoglycemic agents in Japan. Although a relationship between the efficacy of DPP-4 inhibitors and the body mass index (BMI) has been reported, this relationship is controversial. We investigated whether the BMI value affects the glucose-lowering efficacy of sitagliptin in obese Japanese patients with type 2 diabetes.

Methods One hundred sixty-two outpatients with inadequate glycemic control were divided into four groups based on their baseline BMI values. They were then treated with sitagliptin (a DPP-4 inhibitor) for 3 months and followed-up for 12 months.

Results Sitagliptin significantly reduced the hemoglobin A1c level (HbA1c: -0.71±0.55%) after 3 months, and continued to reduce the HbA1c level until 12 months. There was no significant difference in the efficacy of sitagliptin among the four BMI groups. A multiple linear regression analysis indicated that the factors contributing to the change in the HbA1c level were the baseline level of HbA1c and the homeostasis model assessment of β-cell function (HOMA-β). In terms of the relationship between the baseline BMI value and the efficacy of sitagliptin treatment, the number of patients who responded to sitagliptin treatment after 3 months was lowest in the group of patients with the highest BMI values. A multiple logistic regression analysis revealed that the baseline HOMA-β function and HbA1c level and a baseline BMI value of ≥30 kg/m^2 significantly contributed to the response to sitagliptin treatment.

Conclusion The results indicated that sitagliptin treatment was effective in controlling glucose metabolism disorder in obese Japanese patients with type 2 diabetes. However, the efficacy of sitagliptin treatment might be attenuated in severely obese patients, such as those with a BMI value of ≥30 kg/m^2.

Key words: dipeptidyl peptidase-4 inhibitor, sitagliptin, obesity

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Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). They increase the levels of the endogenous active forms of both GLP-1 and GIP, and enhance insulin secretion in a glucose-dependent manner (1, 2). Type 2 diabetes is a metabolic disorder that is mainly characterized by a decline

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in insulin secretion and the development of insulin resistance. Japanese patients with type 2 diabetes are lean, mainly due to insufficient insulin secretion rather than as a result of insulin resistance (3, 4). At the clinical level in Japan, DPP-4 inhibitors are the most frequently prescribed oral hypoglycemic agents for Japanese patients with type 2 diabetes.

A recent observational study indicated that the prevalence of obese type 2 diabetes has been increasing in Japan over the last decade (5). An increase in body weight is an important problem in the treatment of such individuals, particularly in terms of long-term glucose control. An inappropriate increase in the secretion of insulin and an excessive insulin concentration enhances body weight gain and leads to poor blood glucose control (6, 7). Consequently, DPP-4 inhibitors, which enhance insulin secretion in a glucose-dependent manner and which have the advantage of having a neutral effect on body weight, might be useful for combatting insufficient insulin secretion in obese patients with type 2 diabetes.

However, some Japanese retrospective studies have shown a negative correlation between the glucose-lowering efficacy of sitagliptin (a DPP-4 inhibitor) and the baseline body mass index (BMI) value (8-10). On the other hand, other studies found no relationship between the glucose-lowering efficacy of DPP-4 inhibitors and the BMI (11, 12). Accordingly, the relationship between the efficacy of DPP-4 inhibitors and BMI remains controversial.

We therefore designed a prospective study to investigate whether an individual's BMI affects the glucose-lowering efficacy of sitagliptin in Japanese patients with type 2 diabetes. This study was performed by the Okayama Prospective Observational Study for the Efficacy of Sitagliptin in Obese Type 2 Diabetes (OBESE) investigators.

Materials and Methods

Subjects

Japanese outpatients with type 2 diabetes who were ≥20 years of age, were eligible to participate in the present study if they had inadequate glycemic control (HbA1c [Japan Diabetes Society: JDS] 6.5-10.0%) despite diet and exercise therapy alone or together with oral hypoglycemic agents. The key exclusion criteria were: 1) type 1 diabetes (the presence of an autoantibody or a history of ketoacidosis); 2) a history of severe ketosis, diabetic coma, pre-coma, stroke, myocardial infarction or other severe vascular complications within the 6 months prior to the trial; 3) severe infection or severe trauma at the time of study; 4) a perioperative status; 5) renal dysfunction (a serum creatinine level of ≥1.5 mg/dL for men or ≥1.3 mg/dL for women); 6) treatment with a DPP-4 inhibitor other than sitagliptin, glinide, insulin or sulfonylurea at the following doses at the time of study initiation (glimepilide [>2 mg/day], glibenclamide [>1.25 mg/day] or gliclazide [>40 mg/day]); 7) patients who were currently pregnant or planning to become pregnant; and 8) a history of anaphylaxis in response to sitagliptin.

Study design

This was a multicenter (12 hospitals and six clinics), prospective, no-placebo, cohort study. The patients were divided into four groups based on their BMI values as follows after the each patient confirmed their competence and provided their informed consent: <22 kg/m^2, 22 to <25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/m^2. All of the patients received sitagliptin (50 mg, once daily) at the start of the study. If good glycemic control was not achieved, the sitagliptin dose could be increased to 100 mg once daily, and then other oral hypoglycemic agents could be added as necessary. These changes in treatment were entrusted to the medical attendants at each facility.

The primary endpoint was the change in the HbA1c level from the baseline to 3 months after the initiation of sitagliptin treatment. The secondary endpoints were the change in the HbA1c, fasting plasma glucose (FPG) and 1,5-anhydroglucitol (1,5-AG) levels over 12 months after the initiation of sitagliptin. Participants who suffered from adverse events were immediately excluded from the study and given the appropriate treatment and medical care. The patients were examined before and at 3, 6 and 12 months after the initiation of sitagliptin.

All of the procedures in the present study were carried out in accordance with the institutional and national ethical guidelines for human studies and were conducted in accordance with the Declaration of Helsinki. The ethics committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences approved the study. All patients provided their written informed consent prior to their participation in this study. This study was registered with the Clinical Trial Registry of the University Hospital Medical Information Network (registration number: UMIN000005013) and was performed from February 2011 to March 2014.

Laboratory measures

The patients' background medical information was obtained at the time of enrollment and included the age, gender, BMI, waist circumference, duration of diabetes, and diabetes medications. The patients' body weight and waist circumference were measured when they visited their clinic or hospital. All of the laboratory data were measured at each visit. Blood samples were collected in the morning after fasting. The BMI was calculated as the weight (in kg) divided by height (in m) squared. The homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) and HOMA β-cell (HOMA-β) functions were calculated from the FPG and immuno-reactive insulin (IRI) levels using the following formulas (13):

HOMA-IR=FPG (mg/dL)×IRI (μU/mL)/405

HOMA-β=360×IRI (μU/mL)/(FPG (mg/dL)-63)

All of the laboratory tests were performed at a central

laboratory (SRL, Tokyo) by technicians who were blinded to the treatment allocation. The HbA1c values were measured using a latex agglutination immunoassay and are expressed in National Glycohemoglobin Standardization Program units (14). The plasma glucose levels were measured using the HK-UV method (Kanto Kagaku, Tokyo). The plasma insulin levels were measured using a chemiluminescent assay (CLEIA) (Fujirebio Inc., Tokyo). The serum levels of 1,5-AG were determined using an enzymatic assay (Nippon Kayaku Co., Tokyo), and the glucagon levels were measured using a radioimmunoassay (RIA) kit (Millipore, Billerica, MA, USA). The sample tubes were generally a plain tube, with the exception of the tubes used for glucagon and HbA1c, which contained ethylenediaminetetraacetic acid (EDTA)-2Na with aprotinin and EDTA-2K, respectively. The samples were centrifuged at 1,500 rpm, at 4℃, and then preserved by freezing, with the exception of the HbA1c samples, which were preserved by refrigeration.

Statistical analysis

The values of the continuous variables are shown as the mean ± SD, while categorical variables are shown as the number or percent. Logarithmic transformations were used to normalize the data. A chi-squared goodness-of-fit test was used to determine whether the values were normally distributed. The baseline differences among the groups were analyzed using a one-way analysis of variance (ANOVA) for parametric continuous variables with equal variance and then by Tukey's multiple comparison as a post-hoc test; non-parametric continuous variables without equal variance were analyzed using the Kruskal-Wallis test followed by a Dunn test. Categorical variables were compared using the chi-squared test or Fisher's direct test, as appropriate. Repeated measurements of the HbA1c, FPG and 1.5-AG levels were analyzed using a split-plot design ANOVA, by the Friedman test and then by Dunn's multiple comparison procedure as a post-hoc test for the intrinsic factors of the subjects. A multiple regression analysis or multiple logistic regression analysis was performed to identify the variables that were independently associated with the change in the HbA1c level, or the responsiveness to sitagliptin treatment at 3 months, respectively.

The relationship between the baseline BMI and the efficacy after 3 months of sitagliptin treatment was analyzed based on the following points: 1) whether or not the HbA1c levels after 3 months of sitagliptin treatment were less than the baseline HbA1c level (responder status: patients whose HbA1c levels were reduced in comparison to their baseline values); 2) whether or not the decrease in the HbA1c level (in comparison to baseline) after 3 months of sitagliptin treatment was ≥0.7% (the mean value of the decrease of HbA1c in all patients after 3 months); 3) whether or not the HbA1c levels were equal to or less than the regression line of the ratio of the change in HbA1c after 3 months of sitagliptin treatment; and 4) whether or not the HbA1c levels after 3 months of sitagliptin treatment were reduced to <7.0% at 3 months.

The statistical analyses were performed using the IBM SPSS Statistics 22 software program (IBM, Armonk, NY, USA) and the StatFlex ver. 6.0 software program (Artech Co., Osaka, Japan). p values of <0.05 were considered to indicate statistical significance.

Results

Among the 175 patients who were screened for participation in this study, 13 were excluded because they did not meet the inclusion criteria or because they met the exclusion criteria (n=7), because they withdrew their consent (n=2), or for other reasons (n=4). Thus, 162 patients were enrolled; of these 156 (96.3%) completed the initial 3-month treatment period and 150 (92.6%) completed the 12-month study period (Figure). Twelve patients were withdrawn from the study because they withdrew their consent (n=1), because they exhibited clinical or laboratory adverse events (n=8), or for other reasons (n=3). The adverse events experienced by the patients were generally mild to moderate. They included fatigue (n=1), appetite loss (n=2), nausea (n=1), diarrhea (n=1), eczema (n=1), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation (n=1) and dysgeusia (n=1). All of these symptoms improved after the discontinuation of sitagliptin.

The baseline clinical characteristics of the subjects are shown in Table 1. There were differences among the four patient groups with regard to the mean age, body weight, BMI, waist circumference, duration of diabetes, fasting insulin levels, HOMA-β, HOMA-IR values and the rate at which biguanides were prescribed. The body weight, waist circumference, fasting insulin levels, and the HOMA-β and HOMA-IR values gradually increased according to the BMI. The age of the patients and the duration of diabetes were significantly higher in the three BMI <30 kg/m^2 groups than in the BMI ≥30 kg/m^2 group.

In terms of the efficacy of sitagliptin treatment, sitagliptin achieved a significant reduction in the HbA1c level (-0.71±0.55%, p<0.01) after 3 months of treatment. The HbA1c-lowering effect (-0.64±0.67%, p<0.01) continued until 12 months. The HbA1c reductions of each group after 3 months of treatment were as follows: BMI <22 kg/m^2, -0.59±0.48%; BMI 22 to <25 kg/m^2, -0.70±0.43%; BMI 25 kg/m^2 to <30 kg/m^2, -0.85±0.57%; and BMI ≥30 kg/m^2, -0.59±0.69%.

The reductions in the HbA1c levels of each group after 12 months of treatment were as follows: BMI <22 kg/m^2, -0.39±0.59%; BMI 22 to <25 kg/m^2, -0.67±0.65%; BMI 25 kg/m^2 to <30 kg/m^2, -0.75±0.67%; and BMI ≥30 kg/m^2, -0.64±0.73%. There were significant intragroup differences (in comparison to baseline), but no significant intergroup differences among the four BMI groups (Table 2). In addition, sitagliptin treatment significantly decreased the FPG levels (except in the BMI <22 kg/m^2 group) and the 1,5-AG levels were increased in comparison to the baseline level in

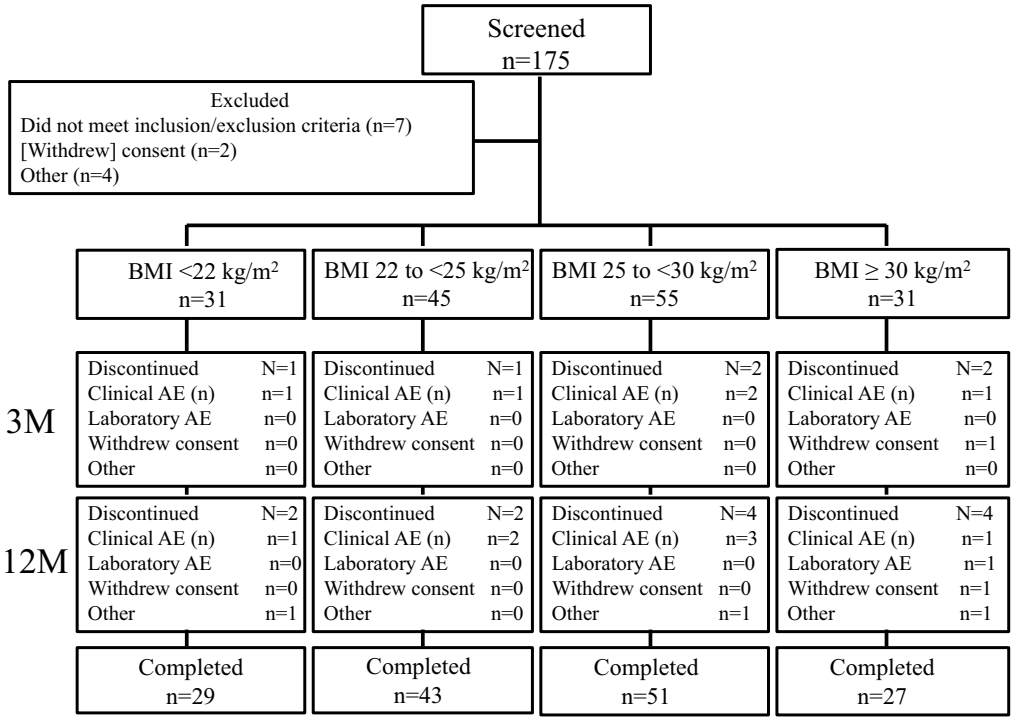

Figure. **The enrollment, grouping and follow-up of the study participants.**

Table 1. **Clinical Characteristics of Subjects at Baseline.**

Characteristic	BMI <22 n=31	BMI 22 to <25 n=45	BMI 25 to <30 n=55	BMI ≥30 n=31	p value
Age (yr)	67±8.3	64.4±7.2	64.1±10.8	52.8±13.3*†‡	<0.001
Female (%)	51.6	42.2	54.5	48.4	0.663
Weight (kg)	49.3±6.6	60.9±7.2*	68.8±9.3*†	89.1±18.0*†‡	<0.001
BMI (kg/m^2)	19.7±1.9	23.7±1.1*	27.0±1.5*†	33.7±4.3*†‡	<0.001
Waist circumference (cm)	75.7±7.6	86.6±5.3*	93.5±6.4*†	105.7±10.9*†‡	<0.001
Duration of diabetes (yr)	9.0±7.8	9.2±6.8	8.1±5.7	4.9±4.7†‡	0.011
HbA1c (%)	7.2±0.4	7.5±0.7	7.5±0.7	7.6±0.9	0.158
Fasting plasma glucose (mg/dL)	137.4±26.3	145.8±36.6	147.0±30.8	150±40.9	0.447
Insulin (μIU/mL)	4.46±5.23	6.37±3.67	8.78±5.46	11.23±5.58	
log(insulin)	1.16±0.80	1.71±0.54*	2.02±0.56*	2.31±0.49*†	<0.001
HOMA-IR	1.53±1.75	2.30±1.46	3.30±2.44	4.25±2.64	
log(HOMA-IR)	0.06±0.84	0.66±0.60*	0.98±0.65*	1.28±0.58*†	<0.001
HOMA-β	22.9±26.9	33.6±29.9	41.3±26.9	56.9±56.0	
log(HOMA-β)	2.79±0.83	3.27±0.67	3.54±0.59*	3.82±0.61*†	<0.001
Glucagon (pg/mL)	71.0±22.9	72.4±19.0	75.5±22.6	83.2±24.1	0.115
1.5-AG (μg/ml)	9.94±8.08	7.63±5.04	7.95±5.34	8.79±6.96	0.680
Any oral hypoglycemic drug (%)	61.3	75.6	67.3	80.6	0.303
Sulfonylurea (%)	32.3	40.0	41.8	19.4	0.169
Biguanide (%)	22.6	44.4	38.2	67.7	0.004
Thiazolidinedone (%)	9.7	26.7	23.6	16.1	0.263
α-Glucosidase inhibitors (%)	25.8	17.8	20.0	16.1	0.780

Values are the means ± SD for continuous variables, and numbers or percentages for categorical variables. See the Statistical Analysis section for an explanation of the methods used to determine the p values.

BMI: body mass index, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model assessment of insulin resistance, HOMA-β: homeostasis model assessment of β-cell function, 1,5-AG: 1,5-anhydroglucitol.

*p<0.05 vs. BMI <22 kg/m^2.

†p<0.05 vs. BMI 22 to <25 kg/m^2.

‡p<0.05 vs. BMI >25 to<30 kg/m^2.

each group, which is consistent with the time course of the HbA1c values (Table 2). There was no significant difference in the change in body weight throughout the study period (data not shown).

To explore the factors that independently contributed to the change in HbA1c at 3 months, we performed a multiple linear regression analysis using the change in HbA1c as an outcome variable and age, gender, duration of diabetes, the

Table 2. Time Course of Glucose Control Parameters by BMI Tertile.

Characteristics	0M	3M	6M	12M	p‡
HbA1c (%)					
BMI <22 (n=25)	7.2±0.4	6.6±0.4 **	6.5±0.4 **	6.7±0.5 **	<0.001
BMI 22 to <25 (n=43)	7.4±0.6	6.7±0.6 **	6.7±0.6 **	6.7±0.6 **	<0.001
BMI 25 to <30 (n=48)	7.5±0.7	6.7±0.7 **	6.6±0.5 **	6.8±0.5 **	<0.001
BMI ≥30 (n=27)	7.6±0.9	7.0±1.1 **	7.1±1.0 **	6.9±0.9 **	<0.001
†p=0.129					
FPG (mg/dL)					
BMI <22 (n=25)	138±26	129±21	131±24	136±30	0.246
BMI 22 to <25 (n=43)	145±36	128±26 **	132±31 **	136±34 *	<0.001
BMI 25 to <30 (n=48)	147±31	132±24 **	132±27 **	133±24 **	<0.001
BMI ≥30 (n=27)	151±42	139±48 *	144±43	132±32 *	0.019
†p=0.853					
1.5AG (μg/mL)					
BMI <22 (n=25)	9.8±8.2	13.8±8.1 **	13.1±8.0 **	12.8±8.6 **	<0.001
BMI 22 to <25 (n=43)	7.8±5.0	13.0±6.9 **	13.0±7.0 **	12.8±7.0 **	<0.001
BMI 25 to <30 (n=48)	7.8±5.4	12.8±7.0 **	13.1±6.6 **	12.0±6.4 **	<0.001
BMI ≥30 (n=27)	8.7±7.1	12.7±8.0 **	11.4±8.3 *	12.1±8.3 **	<0.001
†p=0.866					

Values are the means ± SD for continuous variables. †By split-plot design ANOVA, comparison of groups. ‡Friedman test, comparison of time course. *p<0.05, **p<0.01 vs. 0M by Dunn multiple comparison procedure. BMI: body mass index, HbA1c: hemoglobin A1c, FPG: fasting plasma glucose, 1,5-AG: 1,5-anhydroglucitol

Table 3. Multiple Linear Regression Analysis for the Change in HbA1c after 3 Months.

Independent variables at baseline	Standardized partial regression coefficient	p value
Age	−0.081	0.372
Female	0.056	0.471
BMI	0.100	0.321
Duration of diabetes	−0.106	0.200
HbA1c	−0.508	0.000
HOMA-IR		
log(HOMA-IR)	0.171	0.166
HOMA-β		
log(HOMA-β)	−0.383	0.002
Glucagon	0.079	0.323

baseline BMI, HbA1c and glucagon levels and the HOMA-β and HOMA-IR function as predictive variables. The results of this analysis indicated that the factors contributing to the change in the HbA1c level were the baseline HbA1c level (p<0.001) and the HOMA-β function (p<0.01). The baseline BMI value was not a significant predictor of the change in the HbA1c level (Table 3).

To examine the relationship between the baseline BMI values and the efficacy of sitagliptin treatment, we analyzed the differences in the profiles of the four groups. The results indicated significant differences in the ratio of responders (patients who had reduced HbA1c levels in comparison to the baseline values) among the groups. On the other hand, there were no significant differences in terms of the distribution of 1) patients whose HbA1c level was reduced to a value that was equal to or greater than the mean reduction of HbA1c; 2) those who had a greater response than the regression line of the ratio of change in HbA1c, and 3) those who had achieved an HbA1c level of <7.0% at 3 months (Table 4).

We performed a multiple logistic regression analysis using responder status as an outcome variable and age, gender, duration of diabetes, the baseline BMI value (BMI 22 to <25 kg/m^2: reference group), and the baseline HbA1c and glucagon levels, and the HOMA-β and HOMA-IR function as predictive variables. This analysis showed that the factors contributing to a responder status were the HOMA-β function (p<0.01), the baseline HbA1c level (p<0.05), and a baseline BMI value of ≥30 kg/m^2 (p<0.05) (Table 5).

Only one patient in the BMI <22 kg/m^2 group and one patient in the BMI 22 to <25 kg/m^2 received 100 mg of sitagliptin at 3 months. One patient in the BMI <22 kg/m^2 group, three patients in the 25 to <30 kg/m^2 group, and one patient in the ≥30 kg/m^2 group received additional oral hypoglycemic agents. The conditions for which they were prescribed at 3 months was not significantly related to the responder status (data not shown).

We performed a multiple linear regression analysis to investigate the factors that were associated with the change in HbA1c after 12 months of sitagliptin treatment (Supplementary material 1). The results indicated that the baseline HbA 1c value was the only factor that contributed to the change in the HbA1c value (p<0.001). The baseline BMI value was not a significant predictor of the change in the HbA1c value at 3 or 12 months. In addition, we performed the multiple logistic regression analysis to determine the factors that were associated with responsiveness to sitagliptin treatment after 12 months (Supplementary material 2). This result showed that the baseline HbA1c level was the only factor that was associated with responsiveness (p<0.05).

The pleiotropic effects of sitagliptin treatment, including the blood pressure, lipid profiles and the levels of inflamma-

Table 4. Sub-analysis for Sitagliptin Treatment Efficacy after 3 Months by BMI Tertile.

Sub-analysis	BMI <22 (n=25)	BMI 22 to <25 (n=43)	BMI 25 to <30 (n=48)	BMI ≥30 (n=27)	p value
Patients with a decrease of HbA1c from the baseline (%)	86.7	95.5	94.3	75.9	0.036
Patients with a decrease of HbA1c ≥ 0.7% from baseline (%)	50	52.3	60.4	37.9	0.279
Patients exhibiting a greater response than the regression line of the ratio of change in HbA1c (%)	56.7	50.0	56.6	41.4	0.553
Patients achieving HbA1c < 7.0% (%)	86.7	65.9	67.9	69.0	0.217

p values were compared using a Chi-square test or Fisher's direct test, as appropriate.

Table 5. Multiple Logistic Regression Analysis for the Responsiveness to Sitagliptin Treatment Efficacy after 3-months.

Independent variables at baseline	OR (95%CI)	p value
HOMA-β		
log(HOMA-β)	17.839 (2.742–116.059)	0.003
HbA1c	4.573 (1.224–17.088)	0.024
BMI:		
<22	0.968 (0.123–7.623)	0.975
22 to <25	1	–
25 to <30	0.533 (0.070–4.067)	0.544
≥30	0.074 (0.009–0.613)	0.016
Duration of diabetes	1.144 (0.990–1.321)	0.068
HOMA-IR		
log(HOMA-IR)	0.293 (0.058–1.480)	0.137
Age	1.046 (0.983–1.114)	0.156
Glucagon	1.010 (0.982–1.040)	0.485
Female	0.894 (0.251–3.187)	0.863

tory markers and cytokines are shown in Supplementary material 3. There was no significant change in the blood pressure of the patients throughout the study period. Sitagliptin treatment significantly decreased the cholesterol and low-density lipoprotein (LDL)-cholesterol levels in comparison to their baseline levels, but the efficacy did not continue to 12 months. There was no significant difference in the high-density lipoprotein (HDL)-cholesterol and triglyceride levels. Sitagliptin treatment significantly increased the serum tumor necrosis factor (TNF)-α level in comparison to the baseline level, but the high serum levels of sensitive C-reactive protein (CRP) and malondialdehyde modified LDL (MDA-LDL) did not change to a statistically significant extent.

Discussion

The results of the present cohort study indicate that the sitagliptin treatment was effective in controlling glucose metabolism disorder in obese Japanese patients with type 2 diabetes. The baseline HbA1c level and HOMA-β function but not the baseline BMI value contributed to the change in the HbA1c level after 3 months of sitagliptin treatment. However, the number of subjects who responded to sitagliptin treatment after 3 months was the lowest in the highest BMI group. A multiple logistic regression analysis showed that the baseline HbA1c and HOMA-β values and a BMI of ≥30 kg/m^2 contributed to the responsiveness to sitagliptin treatment after 3 months. The efficacy of sitagliptin treatment after 3 months might thus be attenuated in severely obese Japanese patients with type 2 diabetes, such as those with a BMI value of ≥30 kg/m^2.

In the present study, sitagliptin treatment significantly reduced the patients' HbA1c levels at 3 and 12 months, irrespective of their baseline BMI value, and the change in their HbA1c levels was decreased by approximately 0.7% after 3 months, which is consistent with previous reports (8, 15). In addition, sitagliptin treatment decreased our patients' FPG levels and significantly increased their 1,5-AG levels, which are considered to be a marker of postprandial glucose control. The insulin secretory capacity of Japanese patients with type 2 diabetes is low in comparison to Caucasian patients (4). Accordingly, treatments that augment the secretion of insulin, such as treatments using DPP-4 inhibitors, are pathophysiologically adequate and clinically effective for Japanese patients with type 2 diabetes (16, 17).

The multiple regression analysis showed that the baseline HbA1c and HOMA-β values independently contributed to the change in the HbA1c level after 3 months of sitagliptin treatment. A previous meta-analysis (18) and observational studies involving Japanese patients (8, 15) revealed a higher baseline HbA1c level to be an important predictor of a greater HbA1c reduction following treatment with DPP-4 inhibitors and other oral hypoglycemic agents. Given that the pharmacological action of DPP-4 inhibitors on insulin secretion is glucose-dependent, our results do not contradict this theory.

The baseline HOMA-β function, which is considered a surrogate estimate of pancreatic β-cell function, was another

independent factor in the change in HbA1c after 3 months (13). Based on their mechanism of action, DPP-4 inhibitors may be more effective for patients with preserved pancreatic β-cell function. In fact, the insulin secretion capacity was maintained in the present patients because the HOMA-β function was elevated by sitagliptin treatment (data not shown).

In terms of the relationship between the efficacy of DPP-4 inhibitors and the BMI, it might be necessary to interpret our findings at both the individual and group levels. Our results showed that the change in HbA1c did not differ to a statistically significant extent among the four patient groups who were divided based on their BMI values, and the multiple regression analysis also indicated that the baseline BMI value did not make a significant independent contribution to the change in HbA1c. The group with the highest BMI, (BMI ≥30 kg/m^2) also had the highest baseline HbA1c, and reduction in the HbA1c level in this group was lower than that observed in the other three groups.

In previous reports involving larger cohorts than the present study, or in which most of the participants had BMI values of 22 to <30 kg/m^2, the baseline BMI was related to the HbA1c-lowering effect of sitagliptin (8-10). Thus, in the present study the power of detection might have been somewhat weak. At the individual level, our results indicated that the baseline BMI level was an independent factor that contributed to the responsiveness to sitagliptin treatment. The number of patients who responded to sitagliptin was lowest in our highest BMI group. In a Japanese retrospective study, the baseline BMI was significantly related to responsiveness to sitagliptin therapy (8), which is similar to the results obtained in the present study.

Although the mechanisms by which the efficacy of DPP-4 inhibitors is attenuated in patients with a high BMI value remain poorly understood, two current hypotheses are the release of GLP-1 (19) or the serum concentration of DPP-4 (20) in obese patients with type 2 diabetes are decreased or increased, respectively, in comparison to lean patients. Since the serum DPP-4 concentration has been positively correlated with DPP-4 activity (21, 22), the efficacy of sitagliptin treatment might be attenuated by the elevation of DPP-4 activity in obese patients. In addition, the serum DPP-4 levels were significantly increased in Japanese type 2 diabetic patients with BMI values of ≥30 kg/m^2 in comparison to those with BMI values of <30 kg/m^2 (23). These results might support the idea that the efficacy of sitagliptin treatment was attenuated in the BMI ≥30 kg/m^2 group.

In a recent meta-analysis that aimed to investigate the ethnic differences in the HbA1c-lowering efficacy of DPP-4 inhibitors, a difference in efficacy was observed between the studies of patients with an average BMI value of ≥30 kg/m^2 and the studies of subjects with an average BMI value of <30 kg/m^2 (24). Although the differences in the race of the subjects were taken into account, the HbA1c-lowering efficacy of sitagliptin might change at a BMI value of 30 kg/m^2.

However, the efficacy of DPP-4 inhibitors would be affected by multiple factors, such as the insulin secretion capacity, glucose sensing, GLP-1 release, glucagon suppression and DPP-4 activity, and the efficacy would not be explained by the BMI alone. The GLP-1 levels and the concentration and activity of DPP-4 were not measured in our study. Additional studies are required to investigate the mechanisms underlying the relationship between the efficacy of DPP-4 inhibitors and the BMI.

Among our subjects, biguanide was the most frequently prescribed agent among patients with a baseline BMI of ≥30 kg/m^2. Because DPP-4 inhibitors and biguanides have different mechanisms, the combination of these drugs might have a complementary effect on HbA1c reduction. In a preclinical experiment, the combination of DPP-4 inhibitors and biguanides enhanced the expression of the genes encoding the receptors for both GLP-1 and GIP in mouse islets, and increased the effects of GLP-1 and GIP on insulin secretion from pancreatic β-cells (25). However, our results showed that the prescribed baseline conditions were not significantly associated with the change in HbA1c and that they adversely attenuated the efficacy of DPP-4 inhibitor treatment (data not shown).

There were differences in the factors that contributed to the efficacy of sitagliptin treatment at 3 months and 12 months. In general, the blood-glucose lowering effect of hypoglycemic agents is observed to be affected by a greater number in long-term studies than it is in short-term studies. These factors, including dietary habits, exercise, lifestyle, body weight alterations, the insulin secretion capacity and insulin resistance. In addition, the previous report indicated that sitagliptin treatment efficacy was attenuated during the 12-month study period (26). These ideas might have affected the result. However, the detailed effects are unclear.

This study is associated with some limitations. The study was not blinded and had no placebo group. The sample size was small, which may have weakened the power of detection. Finally, because we did not collect information on the subjects' daily diet, we could not examine the influence of the subjects' dietary behavior or meal contents.

In conclusion, sitagliptin treatment was effective in controlling glucose metabolism disorder in obese Japanese patients with type 2 diabetes. However, the efficacy of sitagliptin treatment may be attenuated in severely obese patients who have a BMI value of ≥ 30 kg/m^2.

Author's disclosure of potential Conflicts of Interest (COI).
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Appendix

The OBESE study was conducted at Okayama University Hospital, Sakakibara Heart Institute of Okayama, Okayama Saiseikai General Hospital, Okayama City Hospital, Okayama Rosai Hospital, Okayama Medical Center, Japanese Red Cross Okayama Hospital, Tsuyama Chuo Hospital, Ochiai Hospital, Konko Hospital, Chugoku Central Hospital, Innoshima Hospital, Osafune Clinic, Asano Internal Medicine Clinic, Shukumo Clinic, Miyajima Clinic, Akebono Clinic, and Hashimoto Kidney Clinic.

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